REMARKS/ARGUMENTS

Claims 1–67 are pending in the captioned application. Claims 4, 6–15, 19, 21, 22 and 51–67 have been withdrawn from consideration. Accordingly, claims 1–3, 5, 16–18, 20, and 23–50 are under consideration in the captioned application.

The Examiner has rejected claims 17, 18, 20 and 23–28 under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention".

Specifically, the Examiner states, "specific to claims 17 and 23-28, line 2, the term 'complementary' causes the claim to be vague and indefinite because it is not clear what criteria are being used to determine that a nucleic acid sequence is complementary to another. Is a complement of 2 nucleotides of two different nucleotides sequence [sic.] sufficient to consider said sequence complementary? Clarification of the metes and bounds is required. Claims 18 and 20 are rejected for being dependent from claim 17".

In response, Applicants respectfully assert that the term "complimentary" is clear to one skilled in the art, and specifically direct the Examiner's attention to page 4, lines 4–11, wherein "complimentary" sequences are discussed. Inasmuch as claim 17 is dependent upon claim 1, which is directed to "a method of selecting a probe for a target

nucleic acid sequence", Applicants respectfully assert that requiring further metes and bounds is improper, as one skilled in the art could easily determine which probes are complimentary and which are not, and no metes and bounds are specifiable.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

The Examiner has rejected claims 1–3,5, 16–18, 20, 23–50 under 35 U.S.C. § 103(a) as "being unpatentable over Manduchi et al. (2000) taken with Allzadeh et al. (2000) in combination with Lockhart et al. (US 6,040,138 A)".

Specifically, the Examiner states, "Manduchi et al. discloses a method for selection of a probe on a microarray for a target nucleic acid sequence wherein two samples types (first composition and second composition) and the ratios from the two separate two-channel microarrays are compared using the same reference for one of the channels…For each homotypic group and for each gene tag, Manduchi et al. computes the average intensity of that tag over a plurality of samples in the group, sets the group in order, establishes a reference group to which other groups are compared, and lists the ratios…"

The Examiner continues, "up regulation is determined by comparing ratio r^1, of the average intensity of a gene tag at group I and the average intensity of the same gene tag at the reference group...The method of Manduchi et al. is applied to hybridizing 3 or more candidate probes...generating datasets containing five homotypic groups comprising human blood progenitor cells..., as in instant claims 1, 3, 5, 20, 29, 31, and 40-50".

The Examiner further continues, "it is noted Manduchi et al. discloses a method directed to highly parallel gene expression experiments,...Although Manduchi et al. demonstrates said method with data generated from a two-channel microarray, said method is applicable to many types of data generated from highly parallel hybridization array experiments. It is well know in the art that a type of highly parallel hybridization array experiment is oligonucleotide arrays wherein gene expression is detected by the complementary of probe sequence to target sequence. The inclusion of a reference by Lipshutz et al. is not being used as prior art but to expand on what is well known in the art of parallel hybridization array experiments...Further, the inclusion of the Duggan et al. reference is not being used as prior art but to expand on what is well known in the art of parallel hybridization array experiments..."

The Examiner concedes, "Manduchi et al....does not disclose the limitations of claims 2, 30, and 32-37". However, the Examiner states, "Allzadeh et al. discloses a

method of generating said data by hybridizing select gene probes on a 'lymphochip' (first

partner) to labeled targets from a cDNA libraries (second partner comprises a label)..."

Further, the Examiner states, "the samples for microarray analysis disclosed by Allzadeh

et al. comprises a low and high concentration and samples are treated in such growth

conditions as phorbol ester, ionomycin, or anthracycline..."

The Examiner further concedes, "Manduchi et al. and Allzadeh et al. do not

disclose the limitation wherein the first or second binding partner comprises biotin". The

Examiner continues, "Lockhart et al. discloses the use of labels such as biotin for nucleic

acids (probe or target) in expression monitoring by hybridization to high-density

oligonucleotide arrays...Lockhart et al. suggests an improvement for monitoring gene

expression via hybridization arrays by using a rapid and effective method for identifying

a set of oligonucleotide probes that maximized specific hybridization efficacy....The

improvement suggested by Lockhart et al. is directly applicable to the method of parallel

gene expression experiments via hybridization arrays..."

The Examiner concludes, "an artisan of ordinary skill in the art at the time of the

instant invention would have been motivated by the improvement suggested by Lockhart

et al. to perform a method of parallel gene expression experiments via hybridization

arrays as taught by Manduchi et al. and Allzadeh et al. using biotin as taught by Lockhart

et al. Therefore, it would have been obvious to one having ordinary skill in the art at the

time of the invention was made to perform method of parallel gene expression

experiments via hybridization arrays with biotin as taught by Manduchi et al., Allzadeh et

al., and Lockhart et al.".

In response, Applicants respectfully submit that the Examiner has misapplied the

teachings of the base reference, Manduchi, et al., to the instant claimed invention.

Specifically, as recited in claim 1, the invention encompasses a method for selecting a

probe for a target nucleic acid molecule comprising seven steps. These steps include

"hybridizing three or more candidate probes with a first composition comprising the

target nucleic acid sequence; determining a first hybridization signal for each candidate

probe; hybridizing the three or more candidate probes with a second composition

comprising the target nucleic acid sequence; determining a second hybridization signal

for each candidate probe; calculating a hybridization signal ratio of the first hybridization

signal to the second hybridization signal for each candidate probe; calculating an average

hybridization signal ratio for the three or more candidate probes; and selecting the

candidate probe by comparing a candidate probe's hybridization signal ratio to the

average hybridization signal ratio".

Thus, the instant invention provides a process for identifying and selecting the

best probe for a specific target nucleic acid sequence.

The Manduchi, et al. paper, on the other hand, discloses (in the abstract) a "protocol...to attach expression patterns to genes represented in a collection of hybridization array experiments". The abstract further states, "our method reflects the broader change of focus in the field from studying a few genes with many replicates to studying many (possible thousands) of genes simultaneously, but with relatively few replicates. Our approach differs from standard methods in that it exploits the fact that there are many genes in the arrays. These are used to estimate for each sample type an appropriate distribution that is employed to control false positives for each of the predictions made. Satisfactory results can be obtained using this method with as few as two replicates".

Thus, the Manduchi, et al. methodology exploits the fact that many assay determinations are being made in parallel, and such determinations may be made with many genes. Indeed, at page 686, column 2, the authors state, "our method exploits the fact that there are hundreds of genes to estimate the appropriate gene independent distribution within each sample type. By integrating over these distributions, false positive rates are calculated directly". Basically, it appears that the Manduchi, et al. reference discloses a methodology whereby the distribution of particular genetic markers, which may number many, but are clearly not the same sequences, can be determined among various cell types. There is no disclosure nor even any suggestion of a

methodology to determine appropriate probes on the basis of the probes' hybridization signal ratio to the average hybridization signal ration of other probes for the same nucleic acid sequence.

Thus, Applicants respectfully submit that the Manduchi reference is directed to a disparate art and neither discloses nor even suggests the instant invention.

The addition of the Allzadeh article and the Lockhart, et al. patent does nothing to remedy this deficiency. Specifically, the Lockhart, et al. patent is mentioned in the Background of Invention section of the captioned application at page, lines 15–22. Specifically, it is stated, "Lockhart *et al.*, …describe…a method…In that…a number of candidate probes to a target sequence are tested to determine which probe provided the strongest signal. In an attempt to account for probes that show a high background signal even in the absence of the target, Lockhart *et al.* compare the probe signal to a signal obtained from a second probe constructed to contain a single mismatch with the target sequence. Only those probes having a signal that is a certain percentage over the signal obtained with the mismatch probe are used. Lockhart *et al.* describe using multiple probes for a given target sequence in an array to accurately determine the expression level of a gene over a range of concentrations".

However, as stated in the captioned application at lines 25, et. seq., "ideally an array would contain only one probe of each gene yet would still be able to provide accurate differential gene expression profiles. Because a probe giving the highest hybridization signal in the given concentration of intended target (chosen by rapid prototyping) [such as in Lockhart, et al.] may not always provide for accurate gene expression profiles wherein different samples having varying amounts or varying structures of the intended target, there is a need for arrays containing only a single probe to each gene yet are still able to indicate variation in the expression level of the gene".

Regarding the Allzadeh, et al. reference, there is similarly no disclosure or even any suggestion of the instant invention. Indeed, while Applicants concede that the Allzadeh, et al. article discloses gene expression profiling, such is quite different from the instant invention.

Further, regarding the Manduchi, et al. article, it is noted that the paper has indicated to be accepted on March 21, 2000. Applicants have learned that the Volume 16, No. 8 Issue was published in August 2000. As such, Applicants responding to the rejection of the Examiner should not in any way be considered as an acquiescence on the part of the Applicants that the Manduchi, et al. reference is properly prior art to the captioned application.
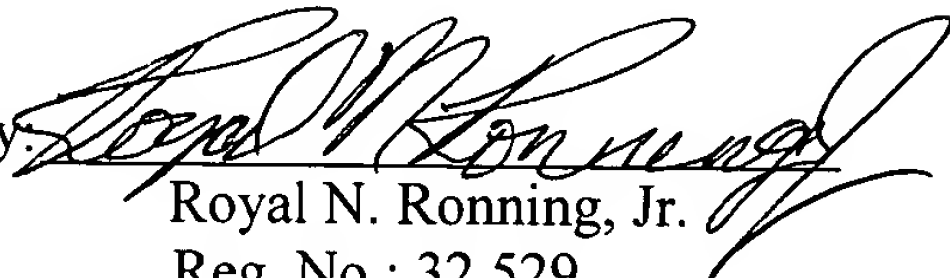
In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be withdrawn.

Applicants believe that the claims are in proper form and earnestly solicit the allowance of claims 1–3, 5, 16–18, 20, and 23–50.

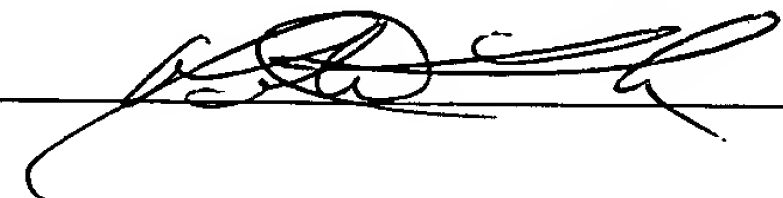Respectfully submitted,

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